Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Annals of Epidemiology 57 (2021) 14–21

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Review Article

COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis

Ana Macedo, MD, PhD[a,b,*], Nilza Gonçalves, MSc[a,c], Cláudia Febra, MD[d]

[a] *Keypoint – Consultoria Científica, Lda, Lisbon, Portugal*
[b] *Departamento de Ciências Biomédicas e Medicina, Universidade do Algarve, Faro, Portugal*
[c] *Nova IMS - Universidade Nova de Lisboa, Lisbon, Portugal*
[d] *Faculdade de Medicina, Universidade do Porto, Porto, Portugal*

ARTICLE INFO

Article history:
Received 6 May 2020
Revised 10 October 2020
Accepted 18 February 2021
Available online 2 March 2021

Keywords:
COVID-19
coronavirus
SARS-CoV-2
outbreak
Mortality
Fatality

ABSTRACT

Background: Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. Although general and local public health report deathly cases, case fatality rates are still largely unknown. Thus, we sought to evaluate the mortality of COVID-19.

Methods: We searched PubMed and EMBASE databases for articles evaluating the clinical characteristics of COVID-19 patients that included clinical outcomes, between December 2020 and 24 April 2020. Two authors performed an independent selection using predefined terms of search.

Results: We retrieved 33 studies with a total of 13,398 patients with COVID-19 diagnosis. The mortality rate of the COVID-19 patients was 17.1% (95% CI 12.7; 22.7, $I^2 = 96.9\%$). For general patients admitted to the hospital (excluding critical care-only studies) the mortality rate of the COVID-19 was 11.5% (95% CI 7.7; 16.9, $I^2 = 96.7\%$). Among critical illness studies ($n = 7$) we found a 40.5% mortality (95% CI 31.2; 50.6, $I^2 = 91.8\%$).

Conclusion: High COVID-19 mortality among general admitted patients and critical care cases should guide resources allocations and economic burden calculations during the pandemics.

Introduction

The first reported case of COVID-19 in Wuhan, China, at the end of 2019, determined the zero point of a timeline that will still go on for several months, not to say years. A fast and widespread outbreak throughout China soon expanded its borders to other countries.

According to the report of the World Health Organization (WHO) as of 7 April 2020, COVID-19 has affected 1,279,722 patients over 212 countries/territories and has caused 72,614 deaths, of which only 6.5% of cases and 4.6% of deaths have been in China [1]. Both the incidence and mortality of COVID-19 vary significantly among different countries/territories and estimation of COVID-19 outcomes during the pandemics is imprecise and, at a certain point, misleading [2,3]. According to China's data, case fatality rate is estimated around 7% in hospitalized patients [4] and 2.3% overall [5]. The numbers resulting from case fatality rate calculations are reached by dividing the number of known deaths by the number of confirmed cases. However, this equation will only be adequate at the end of the outbreak, as the duration of the disease is variable and, especially in the most severe cases admitted to hospitals, may extend several months beyond the initial clinical presentation.

At the present time, several isolated case series reports have been published with preliminary conclusions on risk factors for the COVID-19 related death. Age has soon become one of the main risk factors for death from COVID-19, giving way to all protective measures that all countries are implementing to protect this population from viral transmission, both in the ascending and descending limbs of the local epidemic curves [6]. Deathly outcomes were eventually related to respiratory failure in the vast majority of the patients [7]. In line with this fact, the common early findings on chest CT scans of COVID-19 hospitalized patients are multi-

Conflicts of interest: No conflicts of interest.

* Corresponding author. Alameda Fernão Lopes, 16A, 7ª Andar, Escritório 1, Algés 1495-190, Portugal. Tel.: (+351) 214 096 079; fax (+351) 210 194 675.
E-mail address: amacedo@keypoint.pt (A. Macedo).

https://doi.org/10.1016/j.annepidem.2021.02.012
1047-2797/

lobar and bilateral lesions, patchy ground glass opacities [8,9] that progress to a reticular pattern and will continue a linear evolution to consolidation on unfavorable outcome cases [10].

Apparently, COVID-19 patients with underlying cardiovascular diseases (CVD) have a proven significant increased risk of death, with mortality reaching 10.5% [11] in general Chinese populations. Moreover, the sub-population of hospitalized patients with underlying CVD and escalation of T- troponin levels have shown the highest reported fatality rates [12]. The exact pathophysiological mechanism underlying myocardial injury caused by COVID-19 is not fully understood, but there is growing evidence that COVID-19 patients with previous CVD are more susceptible to a fatal outcome.

The scarcity of detailed data on COVID-19 clinical and outcome characteristics, considering its newness, as well as the universal common efforts from the scientific community to daily reporting on new data on the infection, justify the need for a specific meta-analysis on this particular topic.

Material and methods

Database search and study selection

Two reviewers (CF and AM) systematically and independently searched for clinical studies by using combinations of the following search terms: “covid,” “fatality,” “death,” “mortality,” and “outcome.” The US National Library of Medicine (PubMed) and Excerpta Medical Database (EMBASE) were included in the search, which initially took place in the first week of April 2020 and then was updated with additional information on April 23rd 2020. First, studies that were retrieved were screened according to their titles and abstracts. Only studies on humans were included. Second, the full text of the selected articles was evaluated to make a final determination for inclusion. Finally, the reference lists of the eligible articles were checked for potentially relevant articles (not included in the first online searches). The full texts of these additional articles were also studied for eligibility and possible inclusion. Any discrepancies between the two reviewers were discussed with a third reviewer (NG) until a consensus had been achieved.

In total, 33 published clinical studies were included in the current review for quantitative analyses. The first electronic online database search revealed 231 articles for evaluation, of which 98 full-text articles were retrieved for further adjudication and full-text review after the removal of duplicates and reviews and after title and abstract screening. Two more articles were retrieved from the reference list of relevant articles, which were then included in the final review as well. We considered reasons for exclusion of quantitative analysis the following: home care-only population ($n = 1$), ambulatory-only population ($n = 1$), pregnancy only ($n = 1$) and healthcare providers ($n = 1$), reaching a total of 33 studies for final analyses. Different phases of the information flow of the review are presented in Figure 1.

Outcome, subgroup analysis, and statistical

Our only outcome of interest was hospital mortality. We conducted 2 subgroup analyses restricted to studies with same characteristics population and a low risk of bias: (1) critical illness subgroup analysis (7 studies); (2) general patients admitted to hospital subgroup analysis (21 studies).

The bias level was estimated using the Cochrane Collaboration risk-of-bias instrument [13].

Single-arm meta-analysis were performed using the statistical software package “meta” in R (version 3.3.3) and for a 5% significance level. Random-effect models were estimated using inverse variance method. Logit transformation was performed on the data and continuity correction of 0.5 was applied in studies were zero frequencies were observed. Heterogeneity among studies was tested using τ^2 statistics and I^2 statistics. Funnel plot was used to detect the publication bias (Supplementary Figure 1). Models were estimated considering all studies, and according with general patients admitted to hospital, critical illness, and severe population (to characterize the population classified as general patients).

Results

Study characteristics

Most studies have limitations regarding quality and design with substantial qualitative heterogeneity among them. The 33 included studies analyzed 13,398 patients, 60% were male. Three studies have not specified the age of the participants and just for five studies the mean age of the participants was below 50 years old. The age of participants varied between less than one year and 107 years.

The majority of the included studies were from China (82%), representing 45% of all patients; other studies originated in the USA ($n = 3$), Thailand ($n = 1$), Italy ($n = 1$) and Spain ($n = 1$). Sixty four percent ($n = 21$) of the studies report data on general patients admitted to hospital, 21% ($n = 7$) on critical illness cases, and there were single studies on cancer, cardiothoracic, cardiovascular disease, elderly and pediatric patients. Comorbidities were described in 82% of the studies ($n = 27$), diabetes in 96% of this ($n = 26$, range 6%–58%), CVD in 78% ($n = 21$, range 2.3%–53.7%), HTN in 78% ($n = 21$, range 9.5%–56.6%), and COPD in 67% ($n = 18$, range 1.4%–38.5%). The median follow-up duration of the studies was 29 days, with a minimum value of 9 and a maximum of 52 days.

The rate of sever patients in studies described as general population was 20.4% (95% CI 13.7; 29.3, $I^2 = 97.7\%$).

The characteristics, demographic and clinical data of the included studies are shown in Tables 1 and 2.

Study quality appraisal and bias assessment

Mortality rates were highly variable in the included studies (range, 0%–62%), with zero mortality rates reported in the studies with lower follow-up. The study distribution was asymmetrical on both sides of the mean, mainly due to zero mortality studies, raising concerns for publication bias.

Quantitative synthesis of the study findings

Global mortality

A total of 33 studies were included [14–46] with 13,398 patients. The results of the random effects model meta-analysis showed that the mortality rate of the COVID-19 patients was 17.1% (95%CI 12.7; 22.7, $I^2 = 96.9\%$; Fig. 2). No significant heterogeneity was found using Cochran X^2 test for homogeneity at alpha = 0.10.

Mortality in general patients admitted to hospital (excluding critical care-only studies)

A total of 21 studies included general patients admitted to hospital with 10,769 cases. The results of the random effects model meta-analysis showed that the mortality rate of the COVID-19 general patients was 11.5% (95%CI 7.7; 16.9, $I^2 = 96.7\%$; Fig. 3).

Mortality in critical illness patients

Seven studies were included for the analyses of critical illness cases, representing 2379 patients. The results of the random effects model meta-analysis showed that the mortality rate of the COVID-19 critical illness patients was 40.5% (95% CI 31.2; 50.6, $I^2 = 91.8\%$; Fig. 4).

Table 1
Characteristics of studies entered into meta-analysis

Author	Month	Country	City	Local source	Patient Group	Total N	N non survivors	N severe
Peng YD	Mar, 2020	China	Wuhan	Hospital	Cardiovascular disease	112	17	16
Xiao Tang	Mar, 2020	China	Wuhan	Hospital	Critical illness	73	21	73
Guan W-jie	Mar, 2020	China	National	Hospital	General	1590	50	254
Tao Chen	Mar, 2020	China	Wuhan	Hospital	Critical illness	274	113	274
Zhongliang Wang	Mar, 2020	China	Wuhan	Hospital	General	69	5	14
Wang D	Feb, 2020	China	Wuhan	Hospital	General	138	6	36
Yan Deng	Mar, 2020	China	Wuhan	Hospital	General	225	109	95
Kui Liu	Jan, 2020	China	Wuhan	Hospital	General	137	16	–
Tao Guo	Mar, 2020	China	Wuhan	Hospital	General	187	43	–
Shaobo Shi	Mar, 2020	China	Wuhan	Hospital	General	416	57	–
Mingli Yuan	Mar, 2020	China	Wuhan	Hospital	General	27	10	–
Ning Tang	Feb, 2020	China	Wuhan	Hospital	General	183	21	–
Ning Tang	Mar, 2020	China	Wuhan	Hospital	General	449	134	97
Yang-kai LI	Mar, 2020	China	Wuhan	Hospital	Cardiothoracic patients	13	5	7
B. Cao	Mar, 2020	China	Wuhan	Hospital	General	199	44	32
Pavan K. Bhatraju	Mar, 2020	USA	Seattle	Hospital	Critical illness	24	12	24
Kai Liu	Mar, 2020	China	Hainan	Hospital	Elderly	56	3	6
Fei Zhou	Mar, 2020	China	Wuhan	Hospital	General	191	54	66
Sijia Tian	Feb, 2020	China	Beijing	Hospital	General	262	3	46
L. Zhang	Mar, 2020	China	Wuhan	Hospital	Cancer patients	28	8	6
Xiaobo Yang	Feb, 2020	China	Wuhan	Hospital	Critical illness	52	32	52
Chaomin Wu	Mar, 2020	China	Wuhan	Hospital	General	201	44	84
Yu Shi	Mar, 2020	China	Zhejiang	Hospital	General	487	0	49
Lo Il	Mar, 2020	China	Macau	Hospital	General	10	0	4
Matt Arentz	Mar, 2020	USA	Washington	Hospital	Critical illness	21	11	21
Grasselli G	Apr, 2020	Italy	Lombardy	Hospital	Critical illness	1591	405	1591
Zhou Y	Mar, 2020	China	Nanchang	Hospital	General	17	0	5
Du RH	Apr, 2020	China	Wuhan	Hospital	General	179	21	–
Wang Y	Apr, 2020	China	Wuhan	Hospital	Critical illness	344	133	344
Tagarro A	Apr, 2020	Spain	Madrid	Hospital	Pediatric	41	0	4
Pongpirul WA	Apr, 2020	Thailand	Bangkok	Hospital	General	11	0	0
Qian G-Q	Mar, 2020	China	Zhejiang	Hospital	General	91	0	9
Richardson S	Apr, 2020	USA	New York	Hospital	General	5700	553	373

Table 2
Demographic and clinical data of the studies entered into meta-analysis

Author	Month	Total N	Median age* (mean ± SD)	Age		Male	Co-morbidities			
				Maximum	Minimum		HTN	Diabetes	CVD	COPD
Peng YD	Mar, 2020	112	–	–	–	–	Non specified			
Xiao Tang	Mar, 2020	73	67	72	57	45	51.2%	27.4%	31.5%	1.4%
Guan W-jie	Mar, 2020	1590	48.9 ± 16.3	–	–	904	16.9%	8.2%	53.7%	1.5%
Tao Chen	Mar, 2020	274	62	70	44	171	34.0%	17.0%	8.0%	7.0%
Zhongliang Wang	Mar, 2020	69	42	62	35	32	13.0%	10.0%	12.0%	6.0%
Wang D	Feb, 2020	138	56	92	22	75	31.2%	10.1%	14.5%	2.9%
Yan Deng	Mar, 2020	225	69	74	62	73	36.7%	15.6%	11.9%	20.2%
Kui Liu	Jan, 2020	137	57	83	20	61	9.5%	10.2%	7.3%	1.5%
Tao Guo	Mar, 2020	187	58.5 ± 14.7	–	–	91	32.6%	15.0%	11.2%	2.1%
Shaobo Shi	Mar, 2020	416	64	95	21	205	30.5%	14.4%	–	2.9%
Mingli Yuan	Mar, 2020	27	60	69	47	12	19.0%	22.0%	11.0%	–
Ning Tang	Feb, 2020	183	54	94	14	98	non specified			
Ning Tang	Mar, 2020	449	65.1 ± 12.0	–	–	268	39.4%	20.7%	9.1%	–
Yang-kai LI	Mar, 2020	13	60.2 ± 5.6	–	–	10	15.4%	7.7%	30.8%	38.5%
B. Cao	Mar, 2020	199	58	68	49	120	–	11.6%	–	–
Pavan K. Bhatraju	Mar, 2020	24	64	97	23	15	–	58.0%	–	4.0%
Kai Liu	Mar, 2020	56	–	–	–	12	27.8%	16.7%	11.1%	–
Fei Zhou	Mar, 2020	191	56	67	46	119	30.0%	19.0%	8.0%	3.0%
Sijia Tian	Feb, 2020	262	47.5	94	1	127	Non specified			
L. Zhang	Mar, 2020	28	65	70	56	17	Non specified			
Xiaobo Yang	Feb, 2020	52	59.7	–	–	35	–	17.0%	10.0%	8.0%
Chaomin Wu	Mar, 2020	201	51	60	43	128	19.4%	10.9%	4.0%	2.5%
Yu Shi	Mar, 2020	487	46	–	–	259	20.3%	6.0%	2.3%	–
Lo Il	Mar, 2020	10	54	64	27	3	30.0%	30.0%	–	–
Matt Arentz	Mar, 2020	21	70	92	43	11	–	33.3%	42.9%	33.3%
Grasselli G	Apr, 2020	1591	63	70	56	1304	–	17.0%	21.0%	4.0%
Zhou Y	Mar, 2020	17	–	70	18	6	Non specified			
Du RH	Apr, 2020	179	57.6 ± 13.7	87	18	97	32.4%	18.4%	16.2%	–
Wang Y	Apr, 2020	344	64	72	52	179	41.0%	18.6%	11.6%	4.7%
Tagarro A	Apr, 2020	41	3	6	0,9	18	Non specified			
Pongpirul WA	Apr, 2020	11	61	74	28	6	36.0%	18.0%	27.0%	0.0%
Qian G-Q	Mar, 2020	91	50	96	5	37	16.5%	8.8%	3.3%	–
Richardson S	Apr, 2020	5700	63	107	0	3437	56.6%	33.8%	–	5.4%

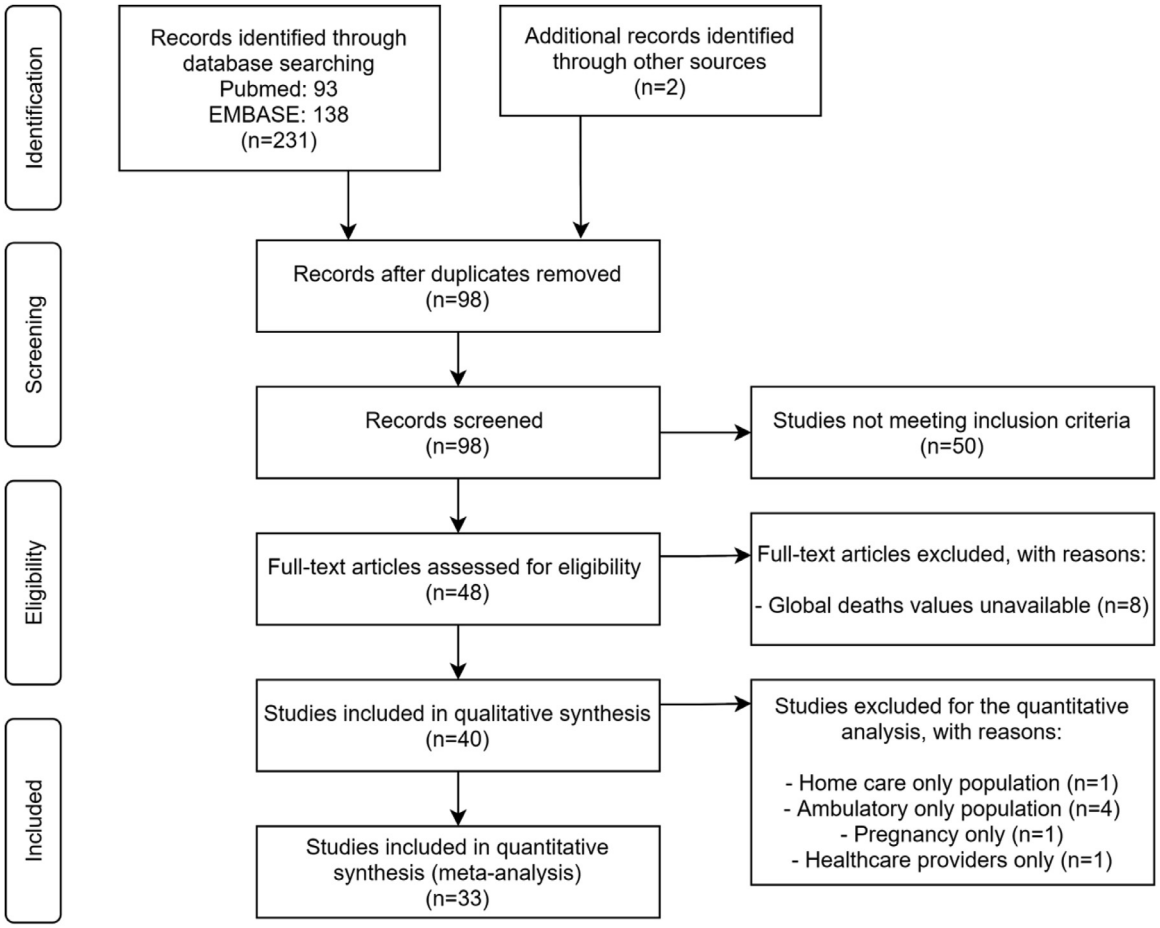

Fig. 1. PRISMA flow diagram for the study selection process.

Discussion

Our systematic review shows an overall 17% mortality rate for COVID-19 patients admitted to hospitals. General reports on death rates for the national populations in the different continents have shown different numbers. At present, the global mortality is 6.73%, thus much lower than the calculated from published studies, and it derives from the available information on confirmed cases and confirmed deaths attributable to COVID-19, worldwide [47] (site Johns Hopkins, accessed on April 17, 2020). This shall be mainly explained by the fact that patients included were predominately hospital admitted patients, being, supposedly, the more severe subgroup of COVID-19 cases.

In our subgroup analyses for patients admitted to hospitals, excluding the studies that reported intensive care-only cases, the mortality rate decreased to 11.5%, reflecting a mixed population effect. This case-mix of all COVID-19 hospital admitted cases included approximately 20% of severe patients who needed highly complex medical assistance and all patients who were admitted for social and public health reasons, irrespective of their clinical severity.

In critical ill COVID-19 patients we report a 40.5% fatality rate, similar to global ARDS outcomes [48]. The respiratory failure has been referred as the main cause for critical care admission of COVID-19 patients and ventilatory assistance is becoming the most illustrative treatment modality for severe manifestations of this acute infection. Although evidence is still growing on the best strategies for mechanical ventilation modes and other vital organ support options, it is evident that high mortality is a characteristic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In our opinion, future research efforts shall be made on gathering worldwide detailed data to contribute to the development of the most effective treatment modalities.

The wider and heterogeneous criteria for the severity classification impose caution in the interpretation of this rate and impact the potential operational measures to address sicker patients admitted to hospitals.

The high incidence of COVID-19 cases during this pandemic justifies current efforts to increase the knowledge on the disease among healthcare professionals and the general public. However, caution should be employed when interpreting our pooled estimates, given the high heterogeneity observed between studies. This variability in estimates could be driven by patient populations' country of origin, as the Chinese-, European- and North American-specific estimates suggest. The different methods of identifying cases, using discharge codes, administrative data, or electronic chart reviews, might also account for some of the differences. For example, some case definition methods may underestimate the diagnosis and significant numbers of patients may be misclassified. The differences observed might also be due to the timing variations in the epidemiology curves of COVID-19 as the time period of the studies varied widely from a single week to several months.

As length of follow-up is associated with different rates of deathly cases, in the way that studies with longer follow-up in-hospital periods tend to report higher rates, we must consider these fatality rates provisional. According to the WHO, recovery time from COVID-19 appears to be around two weeks for mild infections and three to six weeks for severe disease [49]. By se-

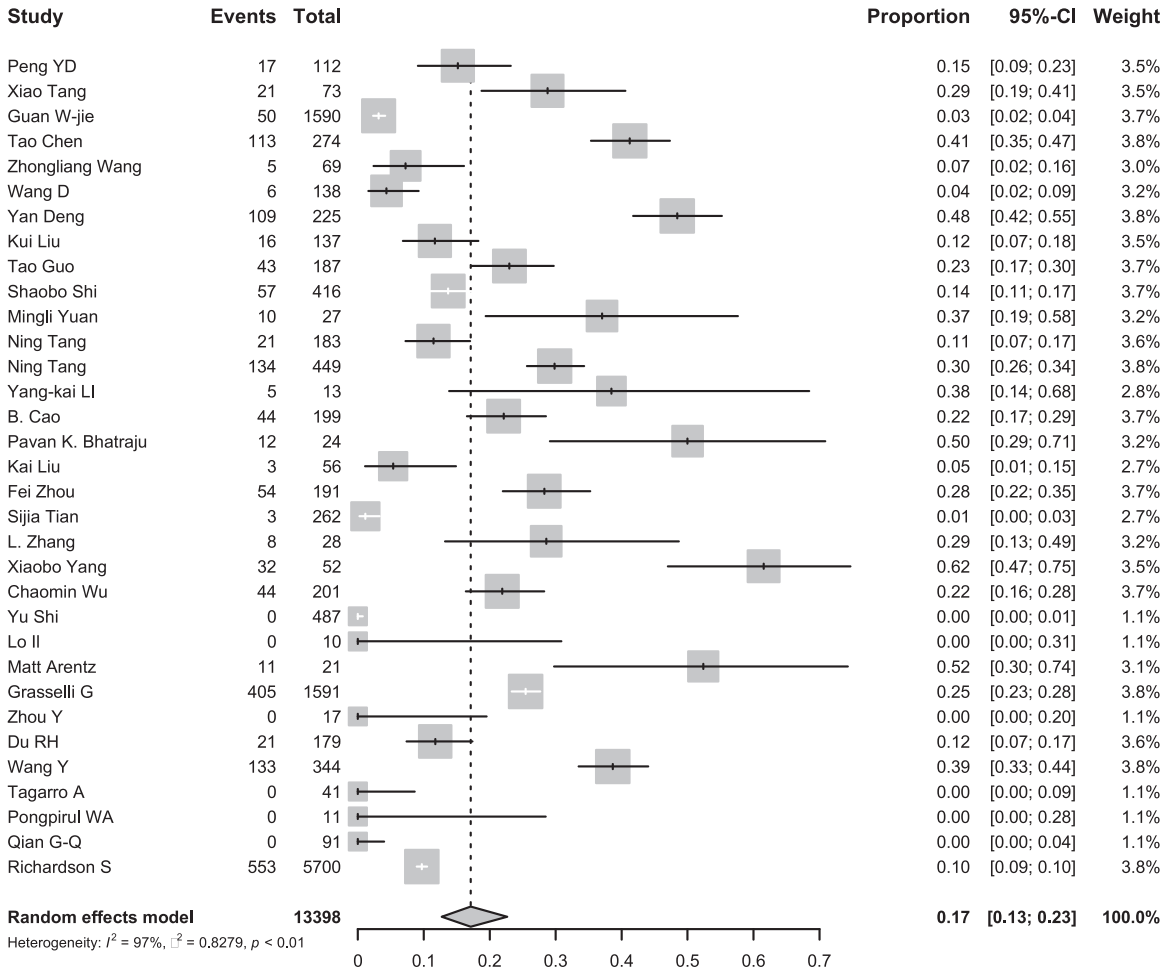

Fig. 2. Global mortality ratio.

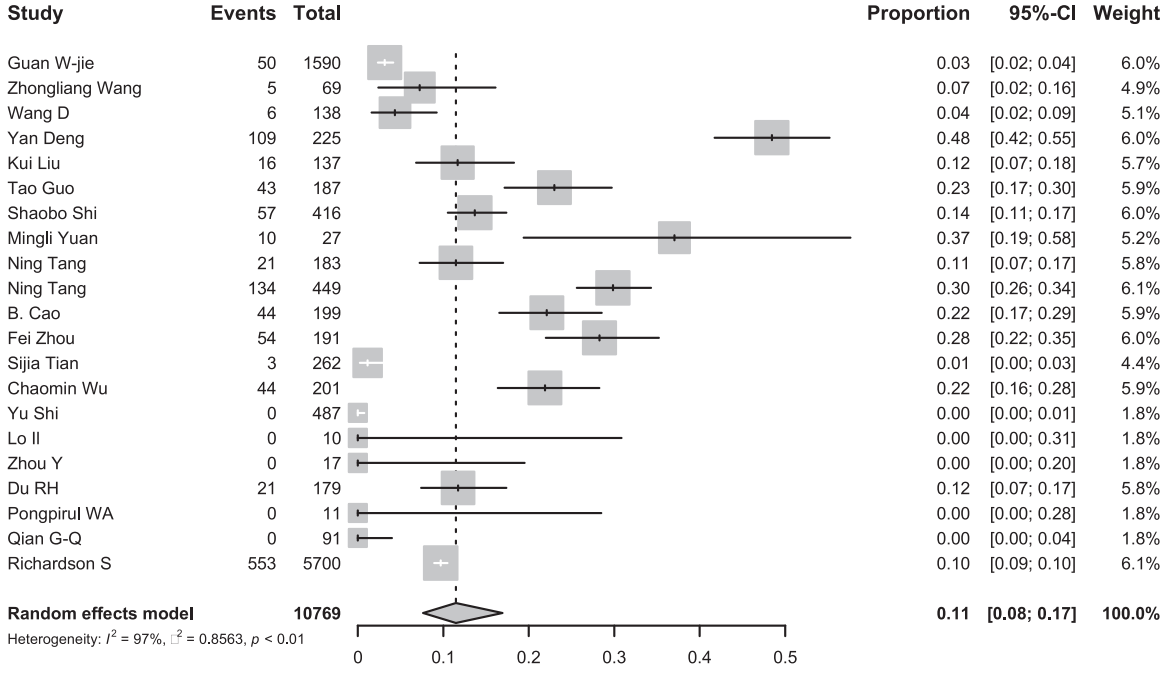

Fig. 3. Mortality in general patients admitted to hospital.

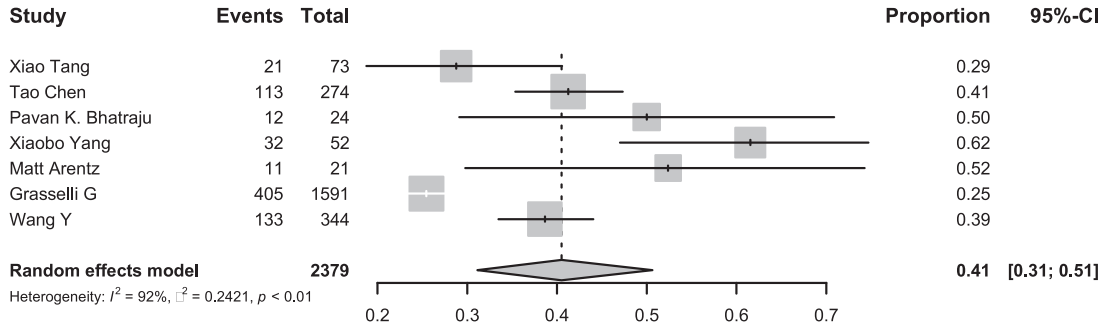

Fig. 4. Mortality in critical illness patients.

lecting studies on hospital series, we are including a proportionally higher fraction of severely diseased, and, consequently, with longer recovery times. The focused and tenacious efforts of the scientific community, from every corner of the world, in readily publishing relevant data on COVID-19 patients, is markedly reducing the duration of follow-up, comparing with usual epidemiologic studies. In these conditions, we shall assume that definite late deaths counting will probably rise global fatality rates, beyond the 17% we report here. The unknown long-term consequences of this emergent disease may well significantly impact on mortality rates, depending on the pathophysiology of its sequelae and, eventually aggravate the already high total economic cost of the disease.

As studies are predominantly originating in China, and the available data on COVID-19 clinical characteristics and all outcomes data coming from other countries concern intensive care patients, we specifically compared critical care populations between Chinese and non-Chinese coming from Washington, United States, and Lombardy, Italy. These analyses revealed that an up-to-date understanding of the COVID-19 associated mortality is important to help guiding resource allocation for countries with a yet to rise number of new cases and, more importantly, for the expected forthcoming phase of repeated outbreaks. Additionally, these information on mortality are critical to inform healthcare budgets, as the economic impact of this pandemic, although still incompletely evaluated, is already known to be have a major impact on healthcare systems all over the world.

The results of our review should be interpreted with consideration of certain limitations. Firstly, we only included studies searched and indexed on occidental databases, potentially leading to language bias as relevant studies published in other languages, such as Chinese or South Korean, were not included. Secondly, the broad range of included studies resulted in a large amount of heterogeneity that could not be fully explained by the variables we assessed. Third, we were unable to specifically examine excess mortality due to co-morbidities, a matter of debate and that justifies further research. Fourth, when looking into the mortality of any acute infectious disease which clinical course may vary from an asymptomatic form to a rapidly fatal outcome, it is of the uttermost importance to classify patients according to the severity of the disease. Unfortunately, we did not have access to gravity scores in most series of patients, nor to the variables necessary to calculate or infer them, thus resulting in a clinical severity heterogeneity that deserves detailed investigation on the upcoming weeks.

In a sense, we believe this study will help to grow the existing basis on the knowledge of a very recent disease and contribute to a better understanding of the dimension of its potentially fatal consequences. Without minimizing the cautious critical judgment on generalizations of epidemiologic studies, the overall fatality of COVID-19 on hospital admitted patients should be taken into consideration in the care of these patients and be one more catalyzer of the ongoing investigation on new treatments and vaccine development.

Conclusion

This analysis reports a higher mortality rate for both mixed-ambulatory and in-hospital patients and in-hospital-only cases. Although we are still missing most of the data on COVID-19 patients, to be published in the near future, these rates shall help to guide resources allocations and economic burden calculations during the present phase of the pandemic.

Declarations

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data included in the review are available under request.

Code availability

Meta-analysis R code are available under request.

Authors' contributions

Ana Macedo: Conceptualization, Methodology, Writing - Original Draft, Supervision.

Cláudia Febra: Conceptualization, Methodology, Writing - Original Draft.

Nilza Gonçalves: Formal analysis, Data Curation, Writing - Original Draft.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2021.02.012.

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